Stem Cell and Neonatology

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Stem Cell History

1998 - Researchers first extract stem cells from human embryos

1999 - First Successful human transplant of insulin-making cells from cadavers

2001 - US President George Bush restricts federal funding for embryonic stem-cell research

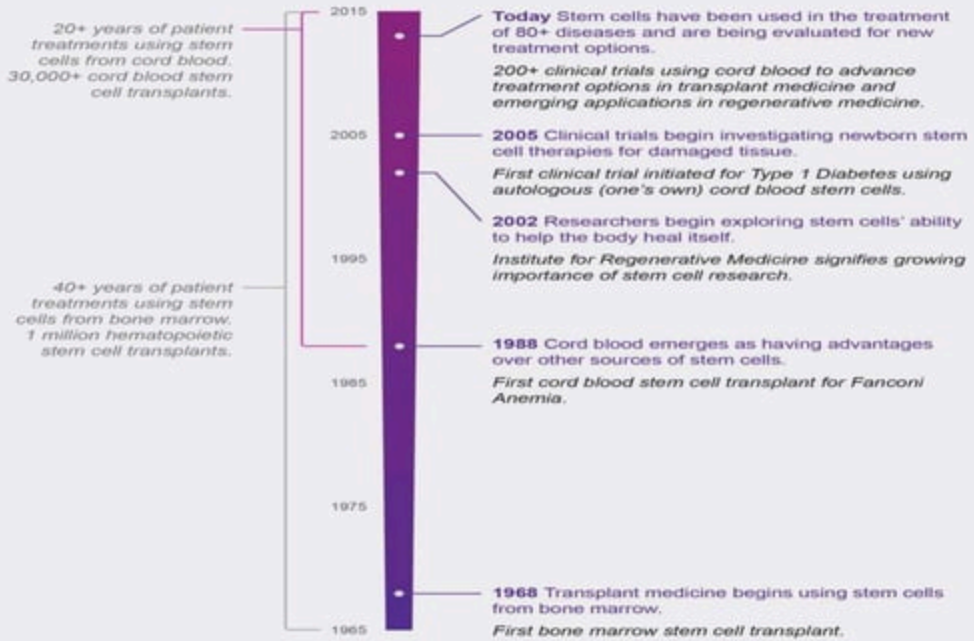
2002 - Juvenile Diabetes Research Foundation International creates $20 million fund-raising effort to support stem-cell research

2002 - California ok stem cell research

2004 - Harvard researchers grow stem cells from embryos using private funding

Stem Cells and Medicine

1 Million Transplants and Counting

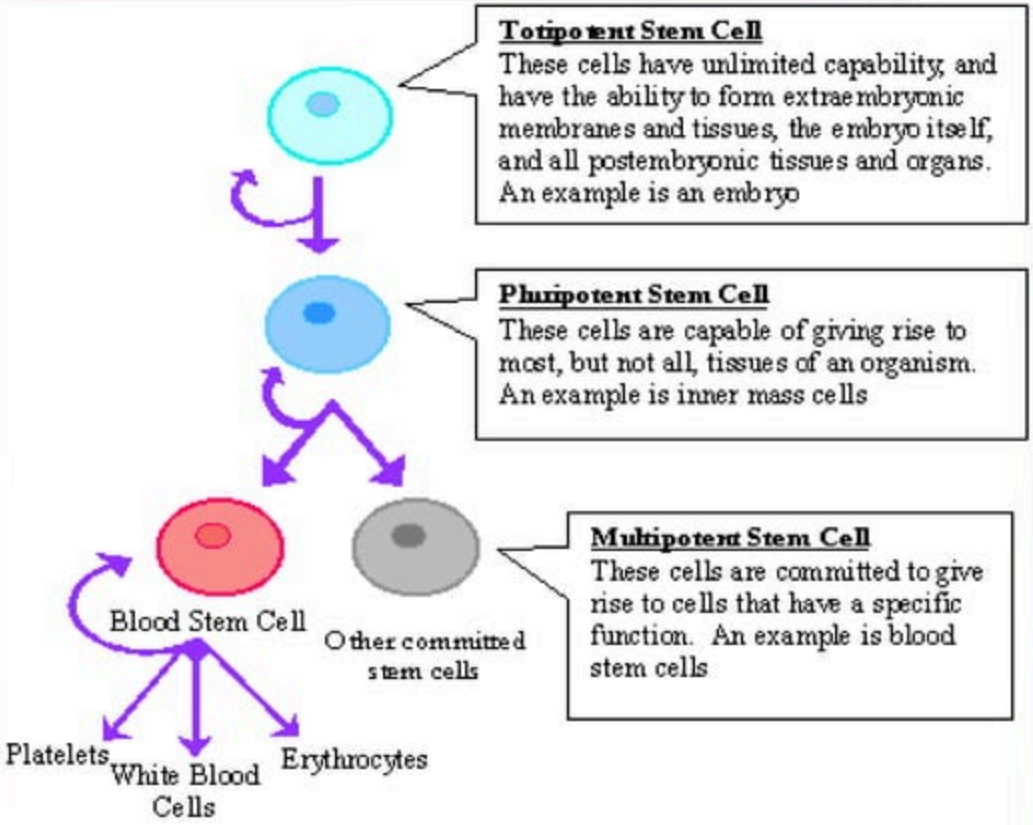


Stem Cell Definition

- A cell that has the ability to continuously divide and differentiate (develop) into various other kind(s) of cells/tissues

Kinds of Stem Cells

Stem cell type	Description	Examples
Totipotent	Each cell can develop into a new individual	Cells from early (1-3 days) embryos
Pluripotent	Cells can form any (over 200) cell types	Some cells of blastocyst (5 to 14 days)
Multipotent	Cells differentiated, but can form a number of other tissues	Fetal tissue, cord blood, and adult stem cells


Totipotent Stem Cell
These cells have unlimited capability, and have the ability to form extraembryonic membranes and tissues, the embryo itself, and all postembryonic tissues and organs. An example is an embryo
Pluripotent Stem Cell
These cells are capable of giving rise to most, but not all, tissues of an organism. An example is inner mass cells
Multipotent Stem Cell
These cells are committed to give rise to cells that have a specific function. An example is blood stem cells
Blood Stem Cell
Other committed stem cells
Platelets
White Blood Cells
Erythrocytes

Kinds of Stem Cells

- *Embryonic stem cells* come from a five to six-day-old embryo. They have the ability to form virtually any type of cell found in the human body.

- *Embryonic germ cells* are derived from the part of a human embryo or foetus that will ultimately produce eggs or sperm (gametes).

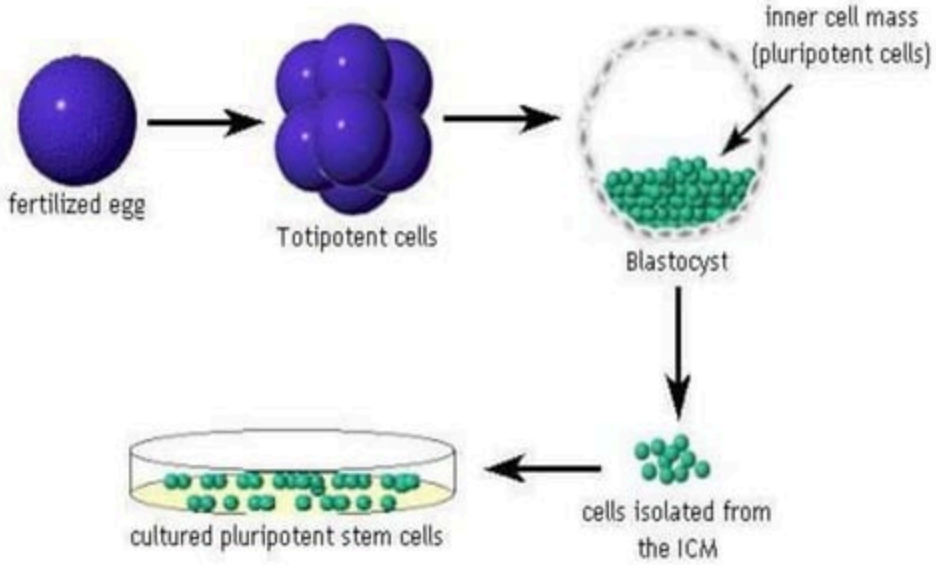
- *Adult stem cells* are undifferentiated cells found among specialized or differentiated cells in a tissue or organ after birth. Based on current research they appear to have a more restricted ability to produce different cell types and to self-renew.

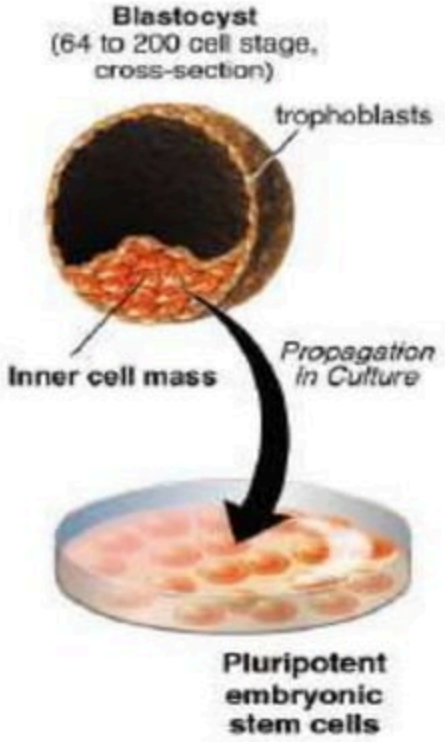
	Comparison of Stem Cell Sources	Umbilical Cord	Adult	Embryonic
1	Ability to differentiate into various cell types	✓	✓	✓
2	High proliferation capacity	✓		✓
3	Low risk of tumor formation	✓	✓	
4	Low risk of viral contamination	✓		✓
5	Capacity for autologous transplantation	✓	✓	
6	Established/proven treatment in human patients	✓	✓	

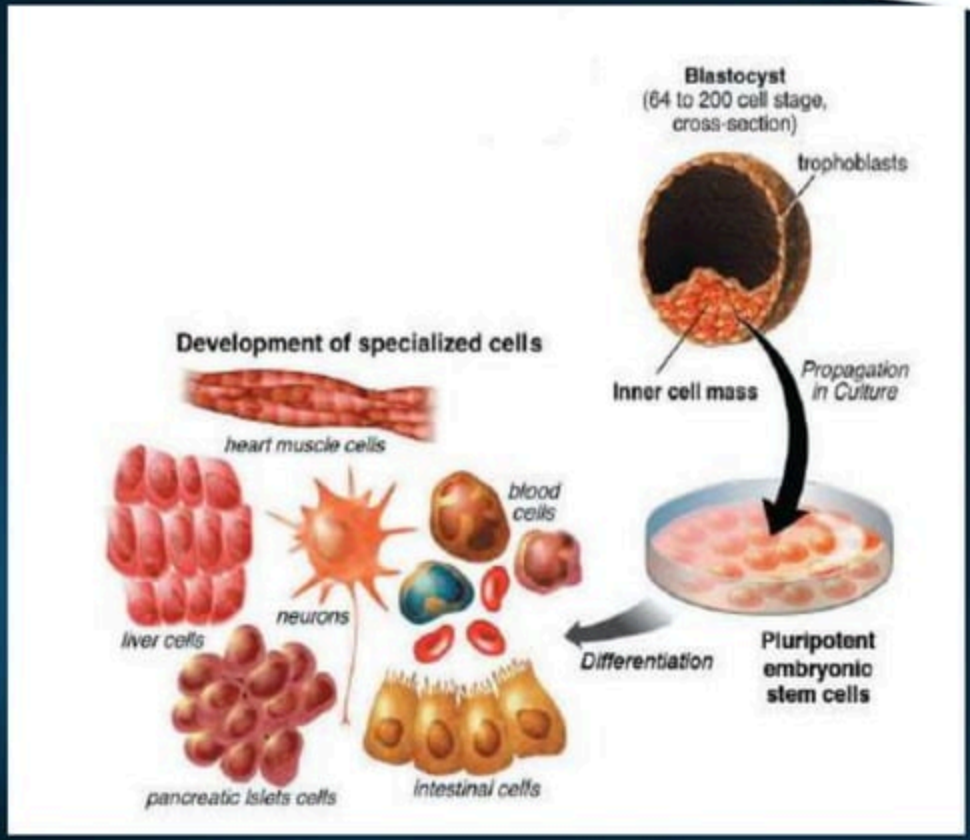
Cord Blood Stem Cells

- Advantage: biologically, a greater degree of human leukocyte antigen mismatch is tolerated by the recipient and the incidence of acute graft-versus-host reaction is decreased when umbilical cord blood is used.
- The predominant disadvantage of umbilical cord blood use is related to the low number of stem cells acquired per unit. However, the use of combined units of umbilical cord blood allows for the expansion of umbilical cord blood volume (and increased number of stem cells) to be used for adult hematopoietic transplants.
- Studies are currently underway evaluating the feasibility of ex vivo expansion of the units

Blastocyst formation




Blastocyst
(64 to 200 cell stage,
cross-section)
trophoblasts
Inner cell mass
Propagation
in Culture
Pluripotent
embryonic
stem cells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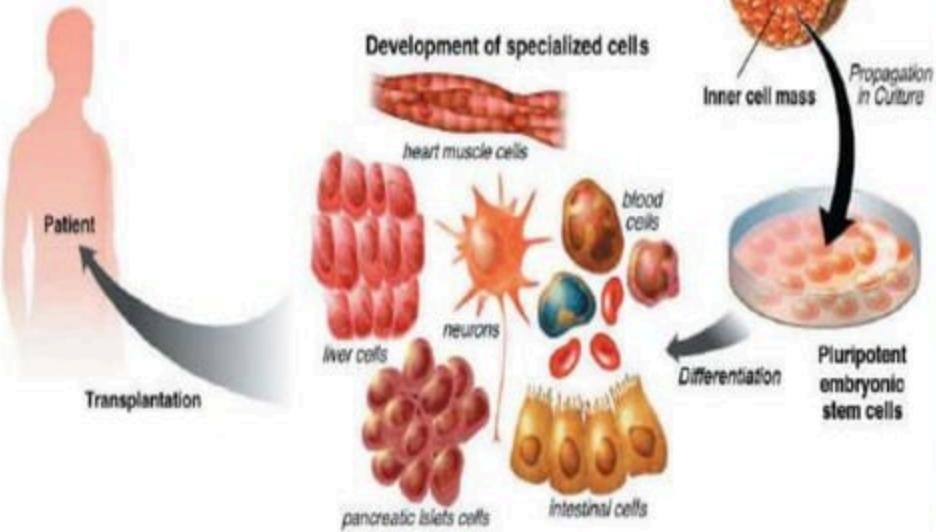
Differentiation
Development of specialized cells
heart muscle cells
blood
cells
neurons
liver cells
pancreatic islets cells
intestinal cells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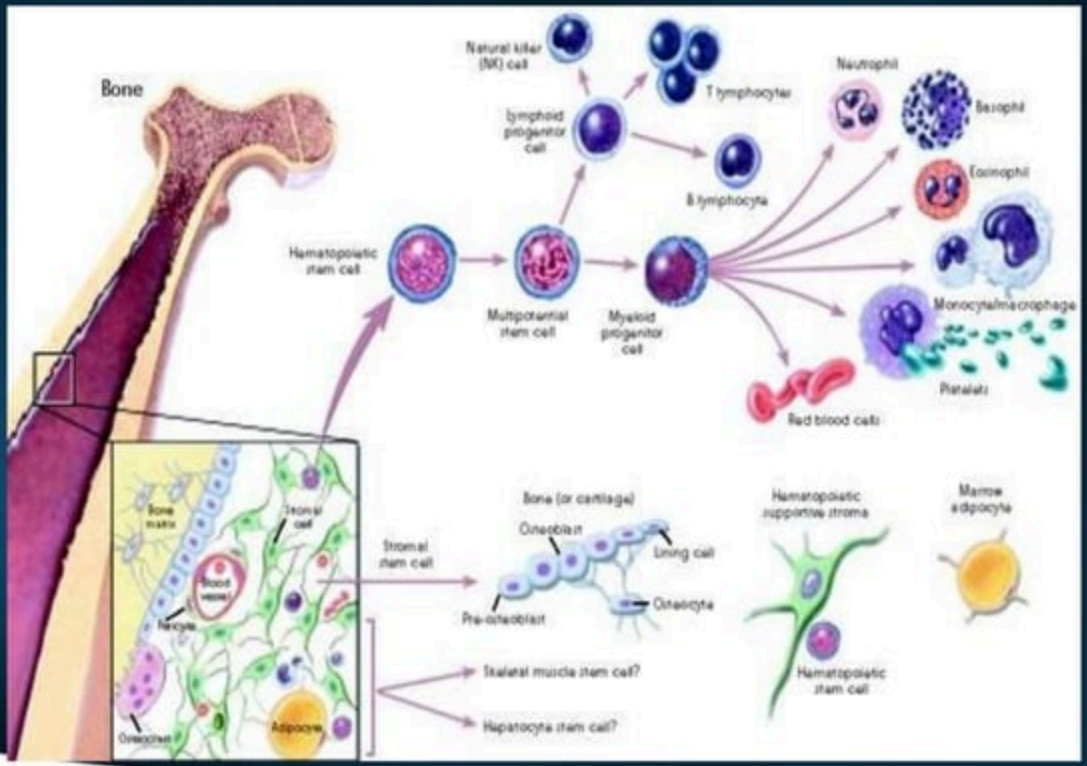
Patient
Transplantation

Adult Stem Cell



- Isolate individual stem cell populations
- Ensure that cells retain their functionality and potential to differentiate

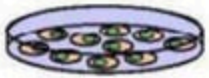
- Characterize & track stem cell populations
- Ensure that cells are "transplant" ready

- Culture stem cell lines in a stable, multi- or pluri-potent state, free from mutations & to sufficient quantity
- Enable Economical expansion to make cell-therapy a reality

- Control & activate stem cell differentiation to desired lineages
- Functionally active differentiated cells

The Promise of Stem Cell Research

Drug Development and Toxicity Tests



Experiments to Study Development and Gene Control

Cultured Pluripotent Stem Cells

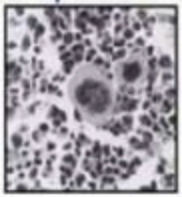
➢Test new drugs on tissues generated from stem cells in vitro.

➢Faster drug development.

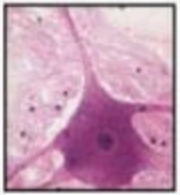
Tissues/Cells for Therapy

➢What is the genetic program that controls cell differentiation?

➢Faster gain in knowledge.

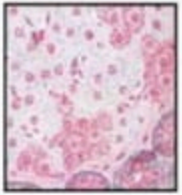


Bone Marrow



Nerve Cells

Heart Muscle Cells



Pancreatic Islet Cells

www.stemcells.nih.gov

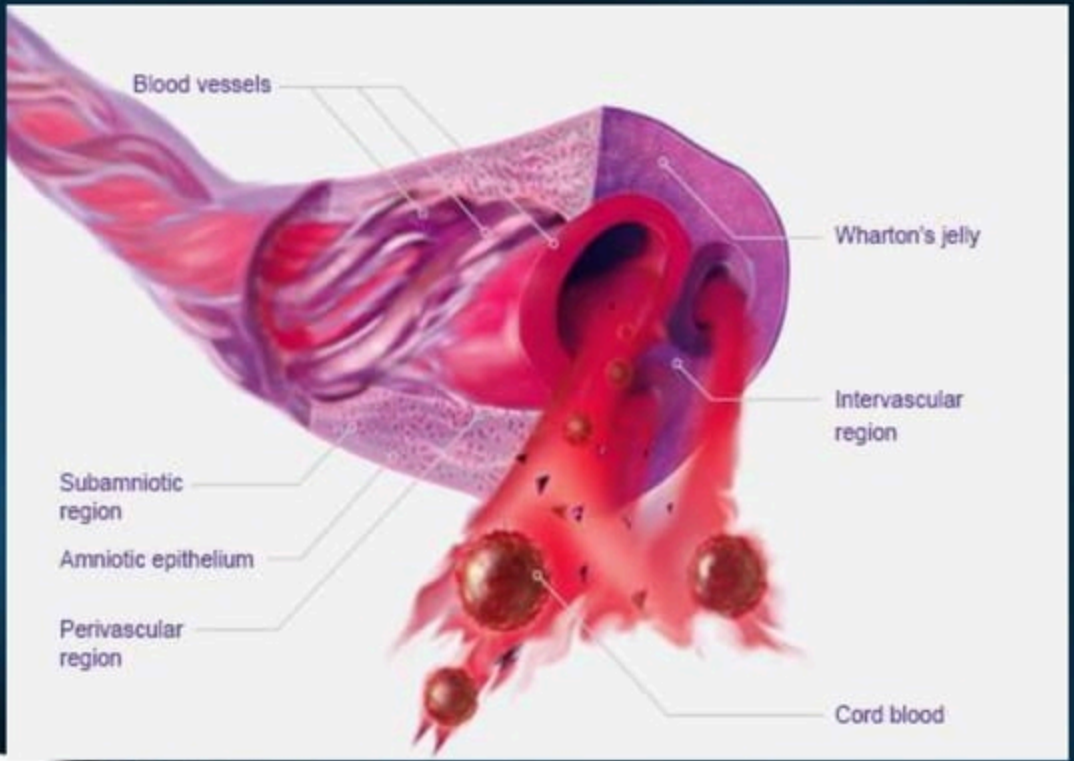
Few diseases treated with stem cells

- **Cancer**
- Acute Leukemia
- Chronic Leukemia
- High-Risk Solid Tumors
- Hodgkin & Non-Hodgkin Lymphoma
- Myelodysplastic Syndromes
- **Blood Disorders**
- Aplastic Anemia
- Beta Thalassemia
- Diamond-Blackfan Anemia
- Fanconi Anemia
- Sickle Cell Disease

- **Immune Disorders**
  - Chronic Granulomatous Disease
  - Hystiocytic Disorders
  - Leukocyte Adhesion Deficiency
  - Severe Combined Immunodeficiency Diseases
  - Wiskott-Aldrich Syndrome
- **Metabolic Disorders**
  - Krabbe Disease
  - Hurler Syndrome
  - Metachromatic Leukodystrophy
  - Sanfilippo Syndrome

(For detail list visit parentsguidecordblood.org)

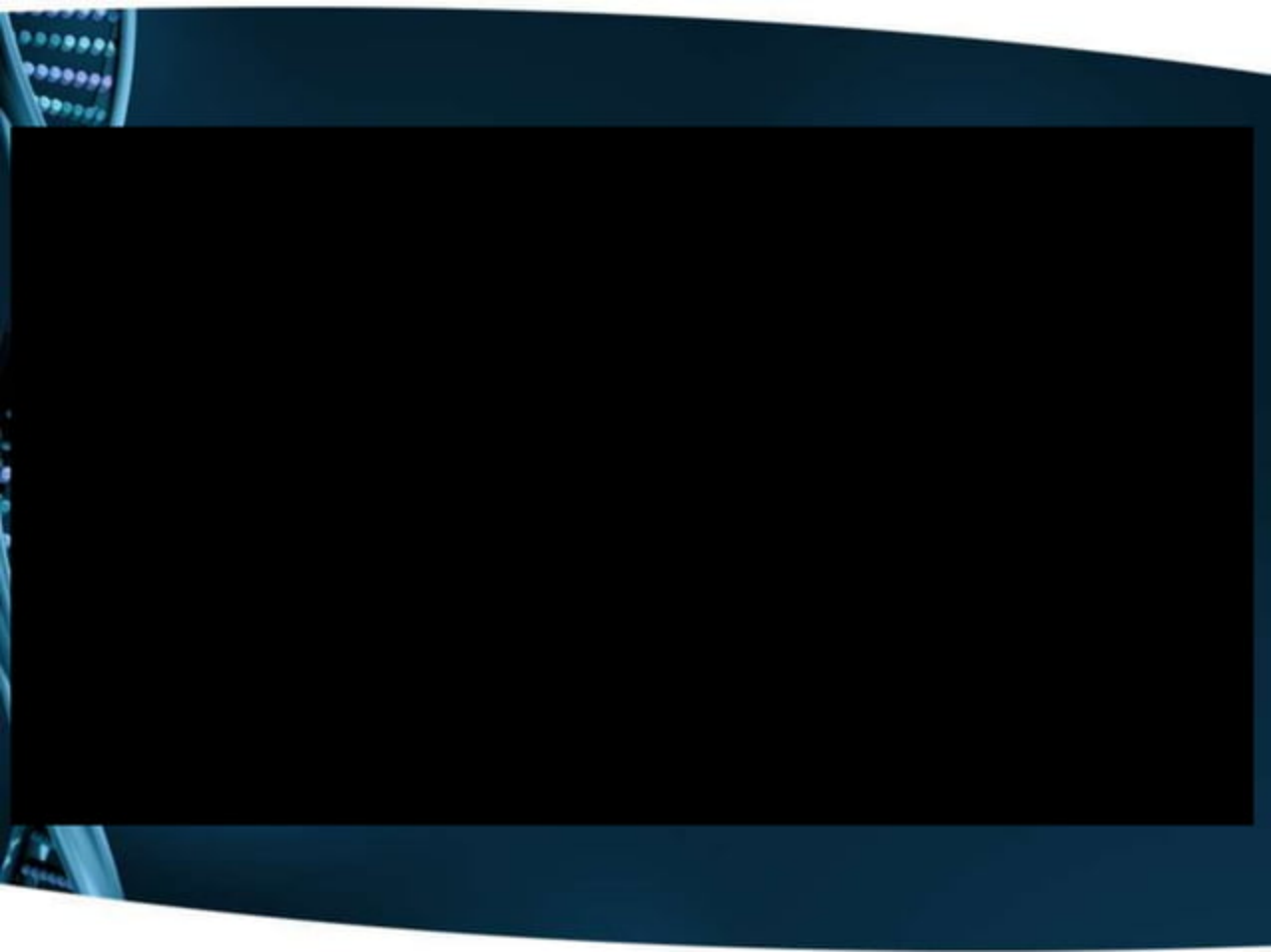
Umbilical Cord




The Best Gift Ever?

Advertising of the Private Banks

- You only have one chance to collect and store your baby's newborn stem cells – immediately after birth.
- After the umbilical cord has been clamped and cut, the remaining blood in the umbilical cord is drawn into a collection bag.
- For families opting to bank cord tissue, a section of the umbilical cord will be collected and stored in the Cord-Cup Container.
- It's important to make a decision about saving or donating well before your due date.
- If you choose to do nothing, your baby's cord blood and cord tissue will be discarded as medical waste.
- Newborn stem cells are not embryonic stem cells. Collecting, storing, and using them is **not** controversial.



Cord Stem Cells

- There are two primary types of newborn stem cells that have the potential to be used for different treatments: hematopoietic and mesenchymal.
- Cord blood predominantly contains hematopoietic stem cells and cord tissue primarily contains mesenchymal stem cells.
- Mesenchymal stem cells differentiate to build bone, cartilage and connective tissue, and they are also very effective at mediating the body's inflammatory response to damaged or injured cells.
- There have been no clinical trials in humans yet that have used MSCs derived from cord tissue. However, over 50 studies have used MSC derived from cord tissue to treat animal models of human diseases, including: Lung Cancer, Parkinson's Disease, Rheumatoid Arthritis, Sports injuries to cartilage, and Type 1 Diabetes.
- Also contains immune cells like dendritic cell, regulatory T- cell and ??Monocyte.

	Mesenchymal Stem Cells	Epithelial and Endothelial Cells
1	Skeletal disease and injury	Wounds, Burns and Ulcers
2	Autoimmune and inflammatory disease	Ocular surface disease
3	Heart and vascular disease	Vascular damage
4	Gastrointestinal disease	
5	Cancer	
6	Diabetes	
7	Transplant Complications	
8	Neurological disease and Injury	

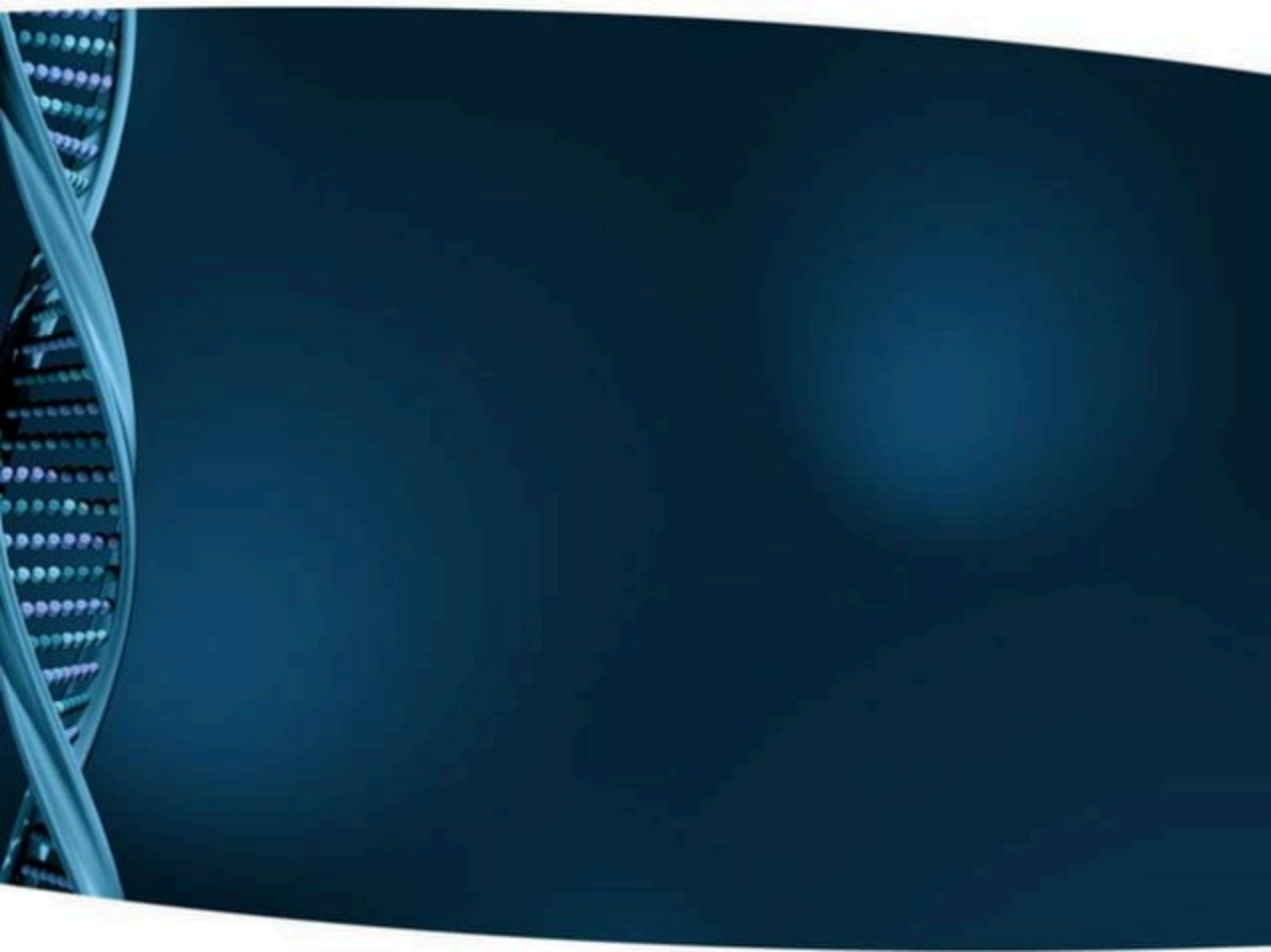
	Cord Blood	Cord Tissue
Primary type of stem cell population	Hematopoietic stem cells (HSCs), which create blood and immune cells	Mesenchymal stem cells (MSCs), which create connective tissue and bone
Current therapies	**Transplant medicine** Used to treat more than 80 diseases, including various cancers and blood, immune, and metabolic disorders† More than 30,000 cord blood stem cell transplants performed worldwide to date.	Currently no proven therapies, but cord tissue is being evaluated in clinical trials as a therapeutic agent for optimizing hematopoietic stem cell transplantation and in regenerative medicine i.e. tissue repair.

	Cord Blood	Cord Tissue
Current research	**Transplant medicine** Hundreds of clinical trials using cord blood stem cells to help advance hematopoietic stem cell transplantation **Regenerative medicine** FDA-regulated clinical trials - potential treatment for conditions like cerebral palsy, autism, traumatic brain injury, and pediatric stroke. Laboratory research - Alzheimer's disease, lung injury, heart disease, and spinal cord injury.	**Transplant medicine** Ability to minimize transplant complications by improving engraftment rates and reducing the risk of graft versus host disease (GVHD). **Regenerative medicine** Clinical trials - autoimmune disease, liver disease, orthopedic indications, and neurological conditions.

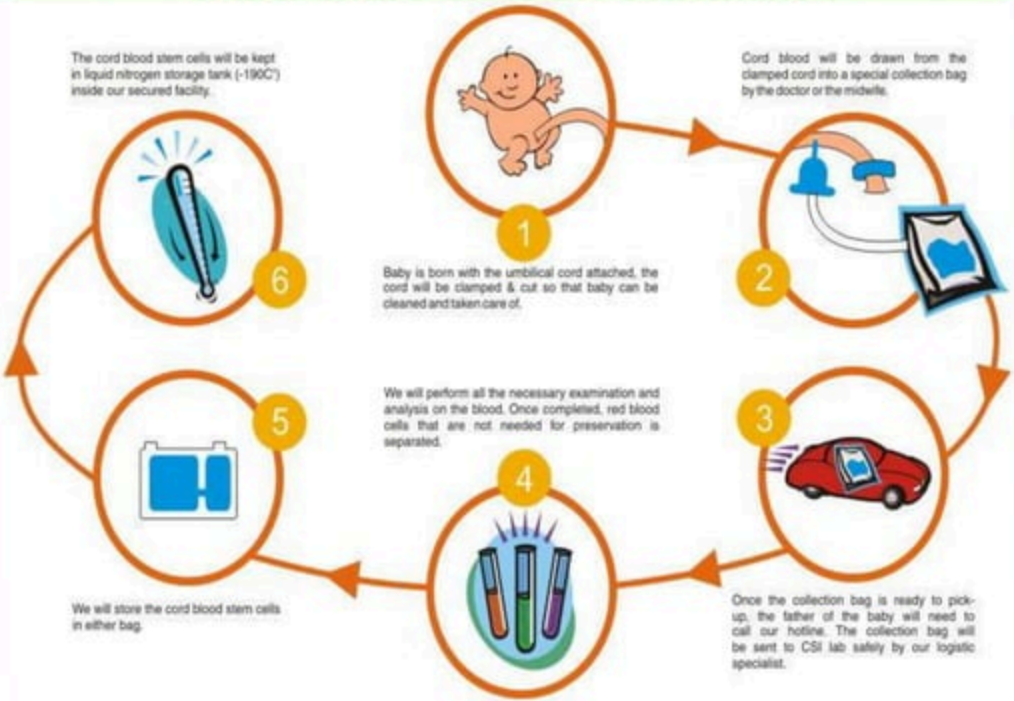
Cord Stem Cell Harvesting

- The method most commonly used in clinical practice is the "closed technique", which is similar to standard blood collection techniques. With this method, the technician cannulates the vein of the severed umbilical cord using a needle that is connected to a blood bag, and cord blood flows through the needle into the bag. On average, the closed technique enables collection of about 75 ml of cord blood.
- Collected cord blood is cryopreserved and then stored in a cord blood bank for future transplantation.
- UCB can be expanded ex vivo over 400-fold by culture techniques that can block cell differentiation with elimination of certain components like copper.
- 3 wk treatment with a copper chelator results in preferential proliferation of a subset of CD34+ cells which seem to be responsible for expansion in long term culture.

Collection



Cord Blood Stem Cell Collection



- Harvesting the tissue of the umbilical cord can yield between 21 million and 500 million MSC.
- A typical cord blood collection in a private bank has a median CD34+ (HSC) count of 1.6 million.
- Currently there is no standard procedure or accrediting criteria for storage of MSC from umbilical cord tissue. Many cord blood banks are storing the cord tissue by freezing an intact segment of the umbilical cord. This procedure has the advantage of waiting for the technology of cell separation to mature, but has the disadvantage that there is no guarantee it will be possible to efficiently retrieve viable stem cells from a previously frozen cord.
- A few cord blood banks are extracting stem cells from the cord tissue before cryogenic storage. This procedure has the disadvantage that it uses the current separation method, but the advantage that it yields minimally manipulated cells that are treatment ready and comply with FDA regulations on cell therapy products.

Public Vs Private Banking

- A cord blood bank may be private (i.e. the blood is stored for and the costs paid by donor families) or public (i.e. stored and made available for use by unrelated donors).
- There are at least 142 public [three in India – Relicord (Reliance Life) Jeevan Cord and Stemcyte and 25 private (seven in India) UCB banks worldwide.
- While public cord blood banking is widely supported, private cord banking is controversial in both the medical and parenting community.
- Although umbilical cord blood is well-recognized to be useful for treating hematopoietic and genetic disorders, some controversy surrounds the collection and storage of umbilical cord blood by private banks for the baby's use.
- Only a small percentage of babies (estimated at between 1 in 1,000 to 1 in 200,000) ever use the umbilical cord blood that is stored.

Current Policy

- .The American Academy of Pediatrics 2007 Policy Statement on Cord Blood Banking states that: "Physicians should be aware of the unsubstantiated claims of private cord blood banks made to future parents that promise to insure infants or family members against serious illnesses in the future by use of the stem cells contained in cord blood."
- Cord blood is stored by both public and private cord blood banks. Public cord blood banks store cord blood for the benefit of the general public.
- Private cord blood banks are usually for-profit organizations that store cord blood for the exclusive use of the donor or donor's relatives.

Cord Stem Cell and Transplant

- At one centre, five year Leukemia Free Survival was 40, 42 and 49 per cent with related donors (RD), well matched unrelated donors (URD) and UCB sources, respectively, while relapse was 31, 17 and 27 per cent in the same group.
- In May 2006 The World Marrow Donor Association (WMDA) Policy Statement for the Utility of Autologous or Family Cord Blood Unit Storage stated that:
- “The use of autologous cord blood cells for the treatment of childhood leukemia is contra-indicated because pre-leukemic cells are present at birth. Autologous cord blood carries the same genetic defects as the donor and should not be used to treat genetic diseases.
- There is at present no known protocol where autologous cord blood stem cells are used in therapy.

- Non- controversial use in some diseases
  - Neuroblastoma, Aplastic Anemia
- Controversial in infancy for leukemias
- ALL – Is the clone present at birth??
  - Detection of clone Vs Detection of leukemic clone
  - Predisposition Vs disease
- AML – Some leukemia specific rearrangements
  - E.g. AML/ETO1 found in 35% of Guthrie spots in children developing AML
- Autologous transplants commonly for adult AML

Metabolic Diseases And Hemoglobinopathies

- In metabolic storage disorders the only therapeutic option is enzyme replacement therapy which is expensive with a long-term requirement. Hence, UCB transplant is desirable and a promising alternative therapeutic option with long term benefits.
- Prasad et al have reported results of 159 pediatric patients with inherited metabolic disorders who received UCB transplant. Engraftment occurred in 87.1 per cent and one year overall survival was 71.8 per cent.
- Increasing use for Hemoglobinopathies, malignancy and inherited diseases
  - Significantly safer than unrelated donor
  - Lower cell dose requirement
  - Lower incidence of GvHD
  - Improved overall survival

Emerging Therapies- Human Studies

- Cerebral palsy
  - Duke “pilot study” is underway
  - “A randomized study of autologous umbilical cord blood Reinfusion in children with cerebral palsy”
- Hydrocephalus
- Hypoxic Ischemic Encephalopathy
  - Characterization of cord blood stem cell in situation of Neonatal Asphyxia – NEOCORD trial
- Hearing loss
- CNS trauma
- Spinal cord injury - Allogeneic

- Cardiovascular trials on
  - Ischemic heart disease
  - Beurger`s disease
  - Congenital heart disease – HLHS
  - In strokes
- Immune trials on
  - Type 1 Diabetes,
  - Rheumatoid Arthritis
  - Crohn`s disease
  - SLE
  - Ulcerative Colitis
  - Multiple sclerosis

Our role as Neonatologist

- If a patient requests information on umbilical cord banking, balanced and accurate information regarding the advantages and disadvantages of public versus private umbilical cord blood banking should be provided.
- The remote chance of an autologous unit being used for a child or a family member (approximately 1 in 2,700 individuals) should be disclosed.
- Discussion may include information regarding maternal infectious disease and genetic testing, the ultimate outcome of use of poor quality units of umbilical cord blood, and a disclosure that demographic data will be maintained on the patient.

- Directed donation of umbilical cord blood should be considered when there is a specific diagnosis of a disease known to be treatable by hematopoietic transplant for an immediate family member.
- The collection should not alter routine practice for the timing of umbilical cord clamping.
- Collection of cord blood should be performed after the delivery of the infant but before delivery of the placenta, using a closed collection system and procedures that minimize risk of bacterial and maternal fluid contamination.

- Physicians or other professionals who recruit pregnant women and their families for for-profit umbilical cord blood banking should disclose any financial interests or other potential conflicts of interest.
- Umbilical cord blood collection should be considered for a sibling or parent in need of stem cell transplantation when an HLA-identical bone marrow cell or peripheral stem cell donation from a sibling or parent is unavailable for transplantation.
- Umbilical cord blood should be considered when allogeneic transplantation is the treatment of choice for a child who does not have an HLA-identical sibling or a well-matched, unrelated adult bone marrow donor .
- Collection and long-term storage of umbilical cord blood for autologous donation is not recommended because of the limited indications and lack of scientific evidence to support the practice.

The Indian story

- India - high birth rate and genetic diversity.
- Nearly 70 percent of patients of Indian origin who require bone marrow transplantation do not find a match within their own family. Hence, unrelated UCB is a widely accepted source of progenitors for hematopoietic stem cell transplantation.
- However, to-date the total number of UCB transplants performed in India has been very low mainly due to high cost and limited number of UCB units available against the estimated requirement of 30,000 units.
- But with the existence of three public UCB banks these figures are likely to improve in the coming years.

- Private banks continue to grow in India, as many families opt to store UCB in private banks with possible advantages in degenerative disorders in the future.
- To meet the future transplantation needs of the country, full participation and substantial investment by the Government is necessary.


THANK YOU